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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,892	05/27/2005	Stefan Golz	Le A 35 944 (004974.01076)	9691
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BANNER & WITCOFF, LTD. 1100 13th STREET, N.W. SUITE 1200 WASHINGTON, DC 20005-4051			HOWARD, ZACHARY C	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/508,892	GOLZ ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 19 February 2009.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-4,6-11,28 and 30 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1-4,6-11,28 and 30 is/are rejected.  
 7) Claim(s) 1-3 is/are objected to.  
 8) Claim(s) 1-4,6-11,28 and 30 are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on 22 September 2004 is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____ .
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date _____.	6) <input type="checkbox"/> Other: _____ .

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/19/09 has been entered.

### ***Status of Application, Amendments and/or Claims***

The amendment of 2/19/09 has been entered in full. Claims 1, 2 and 3 are amended. Claims 25, 27 and 29 are canceled.

Claims 1-4, 6-11, 28 and 30 are pending and under consideration.

### ***Withdrawn Objections and/or Rejections***

The following page numbers refer to the previous Office Action (3/18/08).

All objections and/or rejections of claims 25, 27 and 29 are moot in view of Applicants' cancellation of these claims.

The rejection of claims 1-4, 6-11, 28 and 30 under 35 U.S.C. § 102(b) as anticipated by Bonini et al (2000) at pg 9-13 is *withdrawn* in view of Applicants' amendments to the claims.

### ***Maintained Objections and/or Rejections***

#### ***Claim Objections***

Claim 3 is objected to because of the following informalities:

In claim 3, line 11, the recitation of "is similar to than the activity of the NPFF1 polypeptide" contains the extraneous word "than".

Appropriate correction is required. This objection was set forth at page 14 of the 3/18/08 Office Action. Applicants' 2/19/09 response does not include any response to

this objection, and claim 3 has not been amended to remove the objectionable recitation. Therefore, the objection is maintained.

***Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-11, 28 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was set forth previously and maintained at pg 2-7 of the 3/18/08 Office Action.

Applicants' arguments (2/19/09; pg 5) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that "[t]he Examiner has the initial burden to establish a reasonable basis to question the enablement provided in the specification" (citing *In re Wright* (1999)) and that this requirement has not been met. Applicants argue that the claims are directed to screening methods and not to treatment of disease or cardiovascular disease, nor do the claims require that the tested compounds produce a desirable clinical effect. Applicants argue that it is well known "that not all agents identified in a screening method will become therapeutics and the claims do not require confirmation that the recited test compounds actually can be used to treat any of the recited disease" (pg 5).

Applicants' arguments have been fully considered but are not found persuasive. The initial burden to establish a reasonable basis to question the enablement of the claims was met in the rejection set forth previously. The claimed method is not simply a screening method; instead it is a screening method that recites the intended use of identifying compounds that may be useful in treatment of a cardiovascular disease

(which is the elected species of disease under consideration). If an intended use is recited as part of a claim, it must meet the requirements of 35 U.S.C. 112, first paragraph. Identification of a test compound that can bind to an NPFF1 polypeptide does not allow the skilled artisan to predict whether or not said binding partner can also alter an activity of the NPFF1 polypeptide. A test compound can bind to a receptor without altering its activity. The skilled artisan would still need to test said binding partner in an assay that measured the ability of the binding partner to modulate NPFF1 activity. The specification does not teach a use for binding agents that do not also modulate NPFF1 activity. While not all agents identified in a screening method will become therapeutics, if none of the compounds can achieve the intended use, then the claim has no use. In the instant case, it is unpredictable whether even a single compound that binds to NPFF1, or modulates NPFF1 activity, can be used to treat even a single type of cardiovascular disease.

It is maintained that based on the limited teachings of the specification and prior art, the skilled artisan would not be able to predict whether or not a modulator of an NPFF1-activity (such as alteration of intracellular calcium) could be used to treat a cardiovascular disease. Neither the specification nor the prior art teach provide any reasonable correlation between NPFF1 activity and cardiovascular diseases (either in a general or any species disease). The skilled artisan would recognize that gene expression in a particular tissue does not necessarily indicate that the encoded protein has a role in a disease associated with said tissue. A gene can be expressed in a tissue without having a role in a particular disease associated with that tissue. As shown by Applicants' working examples, NPFF1 is expressed in a wide variety of tissues, with the highest levels of expression in many tissues other than heart tissues. It is possible that NPFF1 activity has a role in said tissues that is entirely unrelated to any disease associated with said tissues. As set forth previously, Juhasz et al (2002; cited previously) demonstrate that thousands of different genes are expressed in tissues of the cardiovascular system (pg 689). The skilled artisan could not predict which, if any, of these expressed genes is associated with one or more cardiovascular diseases. Even if a particular gene is found to have a role in healthy tissue (e.g., healthy heart tissue), the

skilled artisan could not predict whether or not it would also have a role in a cardiovascular disease, such that modulating its activity would treat said disease. As such, it is not predictable whether or not a modulator of NPFF1 could be used to treat one or more cardiovascular diseases. Furthermore, the specification provides no guidance as to whether an agonist or an antagonist of NPFF1 would provide the therapeutic treatment for a cardiovascular disease. In order to use the claimed method to identify a therapeutic, the skilled artisan would need to first practice the claimed method to identify a modulator of the calcium mobilization of NPFF1, and then engage in further undue experimentation to test whether or not the modulator could be used to treat one or more cardiovascular diseases.

In the claim amendments filed 2/19/09, Applicants have added a new method step in independent claims 1 and 2 reciting "iii) measuring the effect of the test compound on a symptom of the disease in an *in vivo* assay..." The new method step in each claim represents an experiment to determine whether compounds that bind to or activate NPFF1 can influence the symptoms of cardiovascular disease(s), and if so, to distinguish which compounds ameliorate or exacerbate said symptoms. The results of such experimentation are not disclosed in the instant specification or prior art. The specification teaches that cardiovascular diseases include a large genus of different conditions including congestive heart failure, myocardial infarction (heart attack), ischemic diseases such as angina, atrial and ventricular arrhythmias, hypertensive vascular diseases, peripheral vascular diseases, and atherosclerosis (pg 55, line 13 to page 57, line 16). Each species of cardiovascular disease has different symptoms. Therefore, the scope of the *in vivo* assay of step (iii) of the claims requires determination of a multitude of different symptoms – essentially a different assay for each form of cardiovascular disease. Thus, the skilled artisan would need to conduct a separate experiment for each "symptom" as recited in the new method step, such experiment being necessary to determine whether any compounds that bind to or activate NPFF1 can treat said symptom. Such experimentation is undue because of the unpredictability of whether any association between NPFF1 binding and/or activity will be found for even one symptom after significant work is performed.

Furthermore, the specification provides little guidance with respect to the symptoms of cardiovascular disease to be monitored in step (iii) of the claims. The specification merely provides a list of various cardiovascular diseases (¶ 175-185 of the published application) followed by a list of tissues of that NPFF1 is expressed in (¶ 186). From these teachings, the specification invites the skilled artisan to modulate the activity of human NPFF1 to treat symptoms of cardiovascular diseases. However, the specification provides little guidance as to the symptoms of cardiovascular disease related to NPFF1 activity that are to be monitored. Thus, undue experimentation would be required by the skilled artisan to identify and monitor all possible symptoms from the plethora of cardiovascular diseases encompassed by the claims.

Furthermore, Applicants' response contains no arguments with respect to the following portion of the rejection set forth previously. Even if the claimed methods were enabled for a method of screening to identify a therapeutic using a polypeptide of SEQ ID NO: 2, they would lack enablement for a method of screening using other variants of SEQ ID NO: 2 for the reasons set forth previously. Each of the amended claims encompasses use of a vast genus of variant "human NPFF1" polypeptides. As set forth previously, the specification teaches that an "NPFF1 polypeptide" includes not only a polypeptide of SEQ ID NO: 2 but also variants which show at least 80% homology to SEQ ID NO: 2, and wherein said polypeptide "has NPFF1 activity" (pg 9, lines 1-15). The polypeptide of SEQ ID NO: 2 consists of 522 amino acids; therefore, a variant with 80% homology has 104 amino acids that differ from SEQ ID NO: 2. The amendment to limit the claims to "human NPFF1" does not change the scope of the claims with respect to SEQ ID NO: 2, because SEQ ID NO: 2 is a human NPFF1 sequence. Prior art was cited teaching that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (Wells (1990); Ngo et al (1995); each cited previously). Prior art was also cited teaching that the art recognizes that function cannot be predicted from structure alone (Bork (2000); Skolnick et al (2000); Doerks (1998); Smith and Zhang (1997); Brenner (1999); Bork et al (1996); each cited previously). In view of the limited teachings of specification regarding the nature of active variants of SEQ ID

NO: 2 and the teachings of the relevant art regarding the difficulty in predicting functional variants of a protein it would require undue experimentation to make and test (for "NPFF1 activity") each member of the vast genus of variants encompassed by the claims.

***Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph, written description***

Claims 1-4, 6-11, 28 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth previously and maintained at pg 7-8 of the 3/18/08 Office Action.

Applicants' arguments (2/19/09; pg 6-8) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the claims have not been construed properly because the claims are limited to a "human NPFF1 polypeptide" and thus "by their plain language" encompass only human NPFF1 polypeptides. Applicants argue that the teaching in the specification that an "NPFF1 polypeptide" includes variants which show at least 80% homology to SEQ ID NO: 2 is therefore not relevant to the invention as now claimed. Applicants argue that the claims must be construed properly (citing *Vas-Cath Inc. v. Mahurkar* (1991)) and that "[i]t is a fundamental rule of claim construction that every limitation is material and that what is claimed is defined by the claim as whole" (citing *General Foods Corp. v. Studiengellschaft Kohle GmbH* (1992)). Applicants further argue (pg 7-8) that the rejection provides "no reasons at all why, in view of the disclosure of the application as filed, a person skilled in the art at the application's priority date would not have recognized that the inventors possessed" the claimed invention and that the "burden of showing that the claimed invention is not described in the application rests on the PTO in the first instance" (citing *In re Edwards* (1978)).

Applicants' arguments have been fully considered but are not found persuasive. It is maintained that the written description rejection set forth previously properly construed the claims and properly set forth fact-based reasons why the skilled artisan would not have recognized that the inventors possessed the full scope of the claimed invention. The specification as originally filed does not define the phrase "human NPFF1 polypeptide"; instead the specification only teaches that the invention provides "human NPFF1" (see Abstract) and that an "NPFF1 polypeptide" includes not only a polypeptide of SEQ ID NO: 2 but also variants which show at least 80% homology to SEQ ID NO: 2, and wherein said polypeptide "has NPFF1 activity" (pg 9, lines 1-15). Nowhere does the specification teach that an NPFF1 polypeptide ceases to be a "human NPFF1 polypeptide" when one or more mutations are made with respect to the naturally occurring sequence of SEQ ID NO: 2. Thus, it is maintained that the phrase "human NPFF1 polypeptide" broadly encompasses variants that differ from SEQ ID NO: 2 by up to 20% and yet retains NPFF1 activity. The polypeptide of SEQ ID NO: 2 consists of 430 amino acids; therefore, a variant with 80% homology has 86 amino acids that differ from SEQ ID NO: 2. Therefore, the genus of polypeptides contemplated by the specification includes those with one or more (up to 86) changes to the amino acid sequence of SEQ ID NO: 2 (including additions, deletions, or substitutions) and which retain an "NPFF1 activity". However, no identifying characteristics of the variant polypeptides are provided such that one of skill would be able to predictably identify which of the variant polypeptides would have the same functional activity as SEQ ID NO: 2. In support of this assertion, the relevant art teaches that that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (Wells (1990); Ngo et al (1995); each cited previously) and that function cannot be predicted from structure alone (Bork (2000); Skolnick et al (2000); Doerks (1998); Smith and Zhang (1997); Brenner (1999); Bork et al (1996); each cited previously). Thus, the instant specification fails to describe the entire genus of variant human NPFF1 polypeptides that will function in the claimed methods (i.e., which mutations of the prior art sequence will retain an "NPFF1 activity"). Therefore it is maintained that only

methods of screening comprising use of a polypeptide of SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

The fact pattern of *General Foods Corp. v. Studiengellschaft Kohle GmbH* (1992), cited by the Applicant and of the instant rejection are significantly different, and the court decisions are not binding with regard to the instant rejections. The decision in *General Foods Corp. v. Studiengellschaft Kohle GmbH* (1992) concerned a double patenting rejection rather than a written description rejection. However, the general statement that "every limitation is material and that what is claimed is defined by the claim as whole" is not disputed. The instant rejection did consider each claim as a whole and that every limitation is material. However, as set forth previously and maintained herein (see above paragraph), the limitation that the NPFF1 polypeptides are "human" does not exclude variants of SEQ ID NO: 2.

Applicants further argue (pg 6) that "even the cited portions of the specification do not support the asserted scope of the recited human NPFF1 polypeptides. The specification defines an "NPFF1 polypeptide" as a polypeptide "selected from a group consisting of" polypeptides having the sequence of SEQ ID NO: 2, polypeptides comprising the sequence of SEQ ID NO: 2, (iii) polypeptides encoded by NPFF1 polypeptides; and (iv) polypeptides which show at least 99%, 98%, 95%, 90% or 80% homology with a polypeptide of (i), (ii), or (iii); wherein said polypeptide has NPFF1 activity. See paragraph [0037] of the published application".

Applicants' arguments have been fully considered but are not found persuasive. Paragraph [0037] of the published application is the same as page 9, lines 1-15 of the specification, which were cited in the rejection as teaching that an "NPFF1 polypeptide" includes not only a polypeptide of SEQ ID NO: 2 but also variants which show at least 80% homology to SEQ ID NO: 2, and wherein said polypeptide "has NPFF1 activity". Applicants quote this paragraph but do not explain how the teachings fail to "support the asserted scope of the recited human NPFF1 polypeptides". This paragraph explicitly states that NPFF1 polypeptides include variants which show at least 80% homology with SEQ ID NO: 2 and have an NPFF1 activity. Thus, it is maintained that this

paragraph supports the scope upon which the rejection is based rather than not supporting said scope.

Applicants further argue that the rejection "sets forth no evidence that the genus of human NPFF1 polypeptides is so varied that the specification does not describe it". Applicants argue that "a specification adequately describes a genus if it permits the skilled artisan to "visualize or recognize members of the genus"" (citing *University of California v. Eli Lilly and Co* (1997)). Applicants argue that the specification describes a human NPFF1 polypeptide comprising SEQ ID NO: 2, and because human NPFF1 polypeptides are highly conserved the species of SEQ ID NO: 2 represents the genus of human NPFF1 polypeptides. In support of this argument, Applicants point to a "BLAST search" of human protein sequences using SEQ ID NO: 2 as a query, and showing that the top 10 search results are "identical to or nearly identical to SEQ ID NO: 2 and are assigned the GENE ID 64106 (NFPP1)".

Applicants' arguments have been fully considered but are not found persuasive. The evidence that "the genus of human NPFF1 polypeptides is so varied that the specification does not describe it" is based on the breadth of the genus (encompassing variants with up to 80% identity to SEQ ID NO: 2) versus the number of species described in the specification (limited to a single species of SEQ ID NO: 2). The genus of polypeptides contemplated by the specification includes those with one or more (up to 86) changes to the amino acid sequence of SEQ ID NO: 2 (including additions, deletions, or substitutions) and which retain an "NPFF1 activity". However, no identifying characteristics of the variant polypeptides are provided such that one of skill would be able to predictably identify which of the variant polypeptides would have the same functional activity as SEQ ID NO: 2. In support of this assertion, the relevant art teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (Wells (1990); Ngo et al (1995); each cited previously) and that function cannot be predicted from structure alone (Bork (2000); Skolnick et al (2000); Doerks (1998); Smith and Zhang (1997); Brenner (1999); Bork et al (1996); each cited previously). It is not disputed that a specification can adequately describe a genus if it

permits the skilled artisan to visualize or recognize members of the genus. However, in the instant case the skilled artisan cannot visualize or recognize which mutations can be made to the sequence of SEQ ID NO: 2 and still retain NPFF1 functionality. Therefore, the specification does not adequately describe the genus of NPFF1 variants encompassed by the claims.

The statement that "human NPFF1 polypeptides are highly conserved" is not understood. The degree of conservation between two sequences refers to the degree of similarity between sequences found within different species (e.g., NPFF1 as found in humans and apes), or between different but similar molecules that are found in the same species (e.g., human NPFF1 and NPFF2). The term "conserved" does not apply to a single sequence from a single species such as human NPFF1. Applicants' first six BLAST search results show six sequences with 100% identity to the 430 amino acids of SEQ ID NO: 2; however, these simply represent the same sequence with multiple accession number records. For example, the record for Q9GZQ6 also contains the accession numbers NP\_071429, AAGr1397 and BAB17677 as cross-references. Furthermore, the other four NPFF1 sequences found by Applicants share 100% identity to SEQ ID NO: 2 over only a portion of the sequence (429, 428 or 386 amino acids). These sequences represent potential allelic variants, splice variants or uncorrected sequencing errors with respect to instant SEQ ID NO: 2. However, neither the instant specification nor Applicants' response provides any information regarding the activity of these variants of SEQ ID NO: 2. Thus, they simply represent a few members of the vast genus of "human NPFF1 polypeptides" encompassed by the claims that may or may not have the functionality of the NPFF1 polypeptide of SEQ ID NO: 2. These results do not provide support for a description of functional human NPFF1 polypeptides in the specification as originally filed.

***New objections and/or rejections***

***Claim Objections***

Claims 1 and 2 are objected to because of the following informalities:

The preamble of each of claims 1 and 2 recites that the method is used for screening for "agents". However, the method steps of each claim employ "compounds" rather than "agents". Either term is acceptable but should be used consistently within the same claim.

Appropriate correction is required.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./  
Examiner, Art Unit 1646

/Bridget E Bunner/  
Primary Examiner, Art Unit 1647